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Dialysate magnesium level and blood pressure

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Dialysate magnesium level and blood pressure.

Background. We investigated the way dialysate magnesium (dMg) concentrations could affect blood pressure (BP) during hemodialysis (HD).

Methods. Eight HD patients underwent four midweek HD treatments consecutively, using, during each four-hour HD session, one of the following four dialysate formulations, in randomized order, which differed only with regard to dMg and dialysate calcium (dCa) concentrations (in mmol/L): 0.75 dMg, 1.75 dCa (group I); 0.25 dMg, 1.75 dCa (group II); 0.75 dMg, 1.25 dCa (group III); 0.25 dMg, 1.25 dCa (group IV). Before HD and at four 60-minute intervals during the HD sessions, BP and noninvasive measurements of cardiac index (CI) were obtained. Additionally, 14 HD patients were treated for four weeks with 0.5 mmol/L dMg, followed by four weeks with 0.25 mmol/L dMg, and another four weeks with 0.75 mmol/L dMg, in random order. In all treatments dCa was 1.25 mmol/L. BP and symptoms were recorded during each HD session.

Results. Mean arterial pressure (MAP) decreased to a significantly ($P < 0.05$) greater extent in group IV compared to the other groups. This substantial drop in MAP by 15.2% in group IV, paralleled by a 12.1% and 17% drop in CI and stroke index, respectively, was not seen in group II, despite comparable reductions in intradialytic serum Mg (sMg) of about 35% in both groups. In groups I and III, the increase in sMg by 2% did not compromise BP via vasodilatation. In the second study, treatment with 0.75 mmol/L dMg was superior to the other two treatments regarding intradialytic morbidity ($P < 0.001$) and BP stability ($P < 0.05$).

Conclusion. We (*1*) identified a dialysis solution containing 0.25 mmol/L Mg and 1.25 mmol/L Ca as a major cause of intradialytic hypotension (IDH) due to an impairment of myocardial contractility, and (*2*) showed that increasing dMg level to 0.75 mmol/L could prevent IDH frequently seen with the use of 1.25 mmol/L dCa. Thus, manipulating dMg levels independently or in concert with dCa levels might have important implications with regard to dialysis tolerance.

Key words: blood pressure, calcium, dialysate, hemodialysis, hemodynamics, magnesium.

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Despite numerous advances in hemodialysis (HD) technology in recent years, intradialytic hypotension (IDH) continues to be a problem with considerable morbidity, occurring in up to 20% of HD treatments. The etiology of IDH is probably multifactorial [1], and therefore, many specific prevention and treatment approaches have been proposed to reduce the incidence of IDH. Manipulating the dialysate composition, mainly sodium and calcium (Ca) concentrations [2–4], is among those of proven efficacy. There are reasons to believe that dialysate magnesium (dMg) levels may also influence intradialytic blood pressure (BP). Mg exerts a direct modulatory action on cardiac excitability and vascular smooth muscle contraction and relaxation [5–6]. Hypomagnesemia has been shown to contribute significantly to cardiac morbidity and mortality, particularly in states associated with myocardial ischemia [7]. Magnesium therapy, both for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving cardiovascular hemodynamics and electrophysiologic functioning. In addition, the vasodilatory effects of the increased serum Mg (sMg) are demonstrated by the BP-lowering effect via a fall in systemic vascular resistance of acute Mg administration in preeclampsia [8]. However, the role of sMg as a potential modulator of the cardiovascular response during HD has not been studied systematically.

sMg increases in advanced renal failure, and in patients on regular HD treatment Mg status mainly depends upon the concentration of dMg. To avoid the development of HD-related hypermagnesemia, potentially induced by high dMg of ≥0.75 mmol/L, low dMg concentrations of 0.25 to 0.5 mmol/L are commonly used today. Current practice utilizes a dCa of 1.25 mmol/L to minimize the risk of HD-induced hypercalcemia caused by high doses of calcium salts and vitamin D given for secondary hyperparathyroidism treatment, along with its related morbidity. However, the use of 1.25 mmol/L dCa has been associated with significant decreases of BP during HD compared to 1.75 mmol/L dCa. Given these considerations, awareness of the way sMg can influence

cardiovascular status during HD, particularly with low dCa of 1.25 mmol/L, would be of paramount clinical importance. In the event that intradialytic hypomagnesemia induced by a low dMg of 0.25 mmol/L demonstrates adverse cardiovascular effects, as recent bibliographic data [9] suggest, then a low dMg of 0.25 mmol/L in the presence of a low dCa of 1.25 mmol/L may put HD patients at a higher risk of developing IDH. On the other hand, the possibility exists that the use of a high dMg of 0.75 mmol/L, by avoiding hypomagnesemia or even causing a slight degree of hypermagnesemia, may exert a positive effect on systemic hemodynamics, capable of partially or completely counteracting the adverse hemodynamic effects elicited with a 1.25 mmol/L dCa, and, consequently, improving HD tolerance.

The aim of the present study was to investigate the effect of dMg modulations on intradialytic hypotension, and to make therapeutic recommendations on the use of dMg level. For this purpose, we examined noninvasively the acute hemodynamic effects of changes in sMg in conjunction with those of ionized serum Ca (iCa) during HD, using different combinations of Ca and Mg concentrations in the dialysate. We chose this model because Mg regulates the activity of vascular smooth muscle cells by competing with Ca [6], and iCa does not remain constant during HD. The objectives of the present study were to identify those dialysate formulations, with respect to Mg and Ca levels, exerting the most or less favorable effects on systemic hemodynamics during HD, and determine the optimal dMg level that could protect against IDH induced by a low dCa of 1.25 mmol/L [10–11].

METHODS

Study A

Eight HD patients, five men and three women, 61 ± 14 years old, were studied. Their mean time on HD was 44 ± 32 months. All patients had uncompromised left systolic function (ejection fraction >40%), no clinical history suggestive of ischemic cardiac disease, no wall motion abnormalities and valve heart disease, based on echocardiographic examination, and normal sinus rhythm. They were clinically and hemodynamically stable, with a hematocrit ranging between 33% and 38%, and a ultrafiltration rate (UF) per treatment equal or less than 3% of their "dry" (or euvolemic) weight, estimated by clinical criteria. The etiology of renal failure was hypertensive nephrosclerosis ($N = 3$), interstitial nephritis ($N = 3$), glomerulonephritis ($N = 1$), and undetermined ($N = 1$). The composition of the dialysate was Na 140 mmol/L, K 2 mmol/L, Ca 1.75 mmol/L, Mg 0.5 mmol/L, bicarbonate 35 mmol/L, acetate 3 mmol/L, and Cl 109.5 mmol/L. None of the dialysis patients were on antihypertensive or other vasoactive drugs during the study period. All patients gave informed consent to participate in the study, which had been approved by the institutional board of General Hospital of Chios.

Study design

All patients underwent four midweek HD treatments consecutively, using, during each HD session, one of the following four dialysate formulations, which differed only with regard to dialysate Mg (dMg) and Ca (dCa) concentrations: dMg 0.75 mmol/L, dCa 1.75 mmol/L (group I); dMg 0.25 mmol/L, dCa 1.75 mmol/L (group II); dMg 0.75 mmol/L, dCa 1.25 mmol/L (group III); dMg 0.25 mmol/L, dCa 1.25 mmol/L (group IV). Between the four intervention studies, patients were treated with their routine dialysis prescription, as described above. The order in which each patient was treated with the four-dialysate formulation was randomly assigned. Only the technician of the dialysis department knew the concentration of Mg and Ca in the dialysate used for each treatment. Dialysis was performed on a volumetric-controlled UF dialysis machine (Gambro AK; Gambro, Lund, Sweden), using polysulfone (Fresenius, Bad Homburg, Germany) low-flux dialyzers (F7HPS, 1.6 m^2). Blood flow was 300 mL/min and dialysate flow was 500 mL/min. The dialysate temperature was 37°C and the dialysate Na concentration was 140 mmol/L. During each of the four intervention treatments, the biochemical and hemodynamic parameters described next were measured.

Biochemical parameters

Arterial blood samples were drawn for biochemical parameters determination before the initiation and immediately after the completion of HD treatment. Sodium (Na), potassium (K), chloride (Cl), iCa, pH, and pCO_2 were measured with the use of a Stat Profile analyzer (Nova Biomedical, Waltham, MA, USA). Serum bicarbonate concentration was calculated from the pH and pCO_2 using the Henderson-Hasselbach equation and pK of 6.1. Total serum calcium (sCa), phosphorus (P), albumins, blood urea nitrogen (BUN), and creatinine were analyzed by usual laboratory methods. A Nova 8 analyzer was used to measure serum ionized Mg (iMg). sMg was measured with a colorimetric method (Cobas Integra System, Roche Diagnostics, Mannheim, Germany), and parathyroid hormone (PTH) was measured using an immunoradiometric assay.

Hemodynamic parameters

Each one of the following hemodynamic parameters was measured before dialysis, and at one-hour intervals during the subsequent four-hour dialysis period. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an automatic blood pressure device (Datex-Ohmeda, Instrumentarium Comp, Helsinki,

Finland), and mean arterial pressure (MAP) was computed as the DBP plus the 1/3 of the pulse pressure. The mean of three consecutive measurements was calculated. Cardiac index (CI), the cardiac output (CO) indexed by body surface area, and heart rate (HR), were derived from thoracic electric bioimpedance (TEB) data, obtained with the NCCOM3-R7/CDDP system manufactured by CardioDynamics International Corp. (Irvine, CA, USA). The validity, limitations, and the reproducibility of the TEB to measure CO have been described by others [12–14]. TEB has been validated [15] and extensively employed for monitoring systemic hemodynamics during hemodialysis [16–17]. Total peripheral resistance (TPR) index (TPRI) was calculated as TPRI = 80 × MAP/CI, where 80 is a conversion factor.

Study B

In this study, we tried to identify the optimal dMg level that could ameliorate or even abolish BP fall, frequently seen upon using a low dCa concentration of 1.25 mmol/L, an effective means to prevent or treat HD-related hypercalcemia. Fourteen HD patients, 10 men and four women, with a mean age of 62.3 ± 12.4 years and a mean time on HD of 55 ± 53 months, participated in the study. All patients were normotensive (BP <140/90) within the last three months, and none of them was on antihypertensive treatment during the study period. IDH, defined as a decrease in blood pressure necessitating fluid replacement therapy, was documented in less than 15% of their regular HD sessions for the three months prior to study participation. Patients' mean interdialytic weight gain was between 1.5 and 2.5 kg, and urine output was less than 300 mL/day. Exclusion criteria were a history of prior myocardial infarction or cardiovascular intervention, symptomatic coronary heart disease, a compromised left ventricular function (ejection fraction 40% or less), a predialysis SBP less than 115 mm Hg, cardiac arrhythmias, and diabetes mellitus. The cause of renal failure was hypertensive nephrosclerosis ($N = 3$), interstitial nephritis ($N = 3$), polycystic kidney disease ($N = 2$), glomerulonephritis ($N = 2$), retroperitoneal fibrosis ($N = 1$), and undetermined ($N = 3$). All patients were treated with vitamin D and $CaCO_3$ supplements for presumed osteitis fibrosa (PTH >400 pg/mL) and were maintained on 1.25 mmol/L dCa and 0.50 mmol/L dMg for more than six months prior to the study. First, each patient underwent a four-week treatment with a medium dialysate Mg of 0.5 mmol/L (MdMg group). After the completion of this four-week HD treatment, all patients were dialyzed, in randomized order, for four weeks with a low dMg of 0.25 mmol/L (LdMg group), and another four weeks with a high dMg of 0.75 mmol/L (HdMg group), separated by an interval of a two-week period, during which MdMg treatment was utilized. In all dialysate formulations, Ca concentration was 1.25 mmol/L and the concentrations of all other ions were the same as in study A. BP and HR were measured before dialysis and every hour during the four-hour dialysis period, and intrasession events were recorded in each treatment. The latter included symptomatic and asymptomatic hypotension. Symptomatic hypotension was defined as the requirement of volume expansion therapy due to either a decrease in SBP of more than 40 mm Hg below the predialysis SBP, a decrease in SBP below 95 mm Hg, or a decrease in blood pressure accompanied by symptoms requiring intervention. Asymptomatic hypotension was defined as a SBP of less than 90 mm Hg without symptoms. Intradialytic symptoms were recorded by the nursing staff, who were blinded to the dMg and dCa. As in study A, only the technician of the dialysis department knew dMg and dCa concentrations used for each treatment. During the second midweek dialysis session of the last three weeks, blood samples were drawn just before the start and immediately after the completion of the HD treatment for sMg and iCa measurement. All dialyses were performed with bicarbonate as a buffer base and with low-flux polysulfone dialyzers (F7HPS, 1.6 m^2 and F8HPS, 1.8 m^2). The rest of dialysis parameters in study B were the same as in study A.

Statistical analysis

Statistical analysis was performed using SPSS/PC 8.0 microcomputer statistical software package (Chicago, IL, USA). Biochemical pre-HD values were compared between groups by using analysis of variance (ANOVA). Within groups, pre- to post-HD changes were evaluated using Student *t* test for paired data. For the analysis of the hemodynamic data, as there were multiple time points for each of the four treatments, a two-factor (time × treatment) repeated measures ANOVA design was used.

In analyzing blood pressure data from study B, a two-factor repeated measures ANOVA design was used as above, except that the blood pressures from 12 sessions were averaged first at each time point prior to analysis. Data were pretested for period and carryover effects during the crossover phase of the study. There was no evidence of period or carryover effect (all $P > 0.396$) of any treatment on sMg, iCa, and blood pressure measurements. Results were similar with and without carryover in the model. For analysis of symptoms, each dialysis session was scored as 0 or 1 for each symptom. We used Cochran's Q statistic to test for differences in symptoms between treatments. For two group comparisons, McNemar test was used instead. Parameters are expressed as absolute values or as percentage changes from baseline. Values are expressed as mean ± SD, unless otherwise stated. The 95% level confidence interval (CI) for the mean is

Table 1. Pre-HD and post-HD data of biochemical parameters and body weight in treatment groups I, II, III, and IV of study A

Parameter	Group I		Group II		Group III		Group IV	
	Pre-HD	Post-HD	Pre-HD	Post-HD	Pre-HD	Post-HD	Pre-HD	Post-HD
sMg *mmol/L*	1.01 ± 0.20	1.01 ± 0.11	1.04 ± 0.18	0.66 ± 0.09[b]	1.05 ± 0.15	1.05 ± 0.11	1.05 ± 0.15	0.69 ± 0.09[b]
iMg *mmol/L*	0.71 ± 0.18	0.70 ± 0.13	0.74 ± 0.13	0.47 ± 0.09[b]	0.71 ± 0.12	0.71 ± 0.10	0.72 ± 0.10	0.47 ± 0.06[b]
iMg/sMg	0.70 ± 0.06	0.68 ± 0.06	0.71 ± 0.04	0.72 ± 0.09	0.68 ± 0.06	0.69 ± 0.06	0.69 ± 0.06	0.68 ± 0.09
sCa *mmol/L*	2.53 ± 0.40	2.67 ± 0.32[a]	2.50 ± 0.39	2.65 ± 0.31[a]	2.48 ± 0.40	2.32 ± 0.19[a]	2.51 ± 0.42	2.28 ± 0.18[a]
iCa *mmol/L*	1.22 ± 0.15	1.29 ± 0.10[a]	1.22 ± 0.17	1.28 ± 0.08[a]	1.22 ± 0.15	1.14 ± 0.09[a]	1.21 ± 0.15	1.11 ± 0. 08[a]
iCa/sCa	0.49 ± 0.02	0.49 ± 0.04	0.49 ± 0.03	0.48 ± 0.03	0.50 ± 0.03	0.49 ± 0.03	0.49 ± 0.02	0.49 ± 0.04
PTH *pg/mL*	237 ± 262	185 ± 256	234 ± 168	182 ± 160	211 ± 148	292 ± 207[a]	248 ± 255	331 ± 357[a]
pH	7.41 ± 0.02	7.47 ± 0.03[b]	7.40 ± 0.02	7.47 ± 0.03[b]	7.41 ± 0.03	7.47 ± 0.03[b]	7.40 ± 0.03	7.48 ± 0.02[b]
PCO_2 *mm Hg*	33.9 ± 3.13	35.1 ± 2.58	34.9 ± 4.56	35.7 ± 3.57	35.3 ± 3.64	36.4 ± 3.69	34.8 ± 3.64	36.6 ± 3.69
HCO_3 *mmol/L*	21.8 ± 2.31	25.9 ± 1.64[b]	22.1 ± 2.8	26.1 ± 2.79[b]	22.7 ± 2.0	26.8 ± 2.41[b]	21.8 ± 2.77	27.3 ± 2.75[b]
Na *mmol/L*	141 ± 2.21	140 ± 1.75	141 ± 3.73	142 ± 1.6	141 ± 1.96	142 ± 0.83	140 ± 2.73	142 ± 1.98
K *mmol/L*	4.65 ± 1.17	3.51 ± 0.49[b]	4.68 ± 1.07	3.53 ± 0.4[h]	4.72 ± 0.63	3.55 ± 0.40[b]	4.74 ± 0.85	3.55 ± 0.36[b]
Cl *mmol/L*	103 ± 2.33	100 ± 1.64[b]	102 ± 0.92	100 ± 1.85[a]	103 ± 1.41	101 ± 1.77[a]	103 ± 1.89	101 ± 1.28[a]
BUN *mmol/L*	80.8 ± 9.2	28.5 ± 5.1[b]	79.5 ± 10.5	26.8 ± 5.4[b]	78.3 ± 8.5	26.9 ± 3.3[b]	79.0 ± 7.2	26.6 ± 4.0[b]
Cr *mmol/L*	856 ± 185	375 ± 102[b]	847 ± 214	392 ± 135[b]	839 ± 183	371 ± 89[b]	827 ± 243	382 ± 128[b]
Albumin *g/dL*	4.01 ± 0.29	4.09 ± 0.31	4.04 ± 0.32	4.18 ± 0.45	3.99 ± 0.34	4.15 ± 0.35	3.98 ± 0.25	4.11 ± 0.43
P *mmol/L*	1.82 ± 0.44	0.8 ± 0.2[b]	1.84 ± 0.42	0.88 ± 0.22[b]	1.83 ± 0.45	0.84 ± 0.25[b]	1.82 ± 0.33	0.84 ± 1.02[b]
BW *kg*	61.1 ± 9.92	59.3 ± 9.81[a]	60.9 ± 9.52	59.3 ± 9.79[a]	61.4 ± 9.52	59.6 ± 9.86[a]	60.9 ± 9.76	59.5 ± 9.87[a]

Abbreviations are: sMg, total serum magnesium; iMg, ionized serum magnesium; sCa, total serum calcium; iCa, ionized serum calcium; PTH, parathormone; Na, sodium; K, potassium; Cl, chloride; BUN, blood urea nitrogen; Cr, creatinine; P, phosphorus; BW, body weight. Data are expressed as mean ± SD.
[a] $P < 0.05$ vs. pre-HD; [b] $P < 0.001$ vs. pre-HD.

also given, where appropriate. Changes were considered statistically significant for P less than 0.05 (two-sided).

RESULTS

Study A

sMg, iMg, sCa, iCa, and PTH were similar prior to the treatments (Table 1). sMg increased slightly by 2.1% (95% CI −5.9 to 10.2) and 2.03% (95% CI −3.6 to 7.6) in the 0.75 mmol/L dMg groups I and III at the end of HD, and decreased significantly ($P < 0.001$) with the use of a 0.25 mmol/L dMg in groups II and IV by 35.6% (95% CI −40.2 to −30.9) and 34.2% (95% CI −38.1 to −30.2), respectively. In treatment groups I and III, sMg increased in four of eight patients, but decreased in the other patients. Almost identical intradialytic changes were observed regarding iMg. Both before and after HD, the correlation between iMg and sMg (total serum Mg) was high ($r = 0.93$; $P < 0.01$ and $r = 0.92$; $P < 0.01$, respectively). In the light of this highly significant correlation between iMg and sMg, we opted to refer only to sMg in the text, since the latter is more widely used in clinical practice and reported in literature. iCa increased ($P < 0.05$) with 1.75 mmol/L dCa in treatment groups I and II by 6.1% (95% CI 0.9 to 11.4) and 6.1% (95% CI 0.6 to 11.5), and decreased ($P < 0.05$) in groups III and IV by 6.4% (95% CI −11.4 to −1.5) and 7.7% (95% CI −13.6 to –1.8), respectively, where the dCa level was 1.25 mmol/L. The correlation between changes in iCa and sCa was high ($r = 0,90$; $P < 0.01$). PTH decreased equally by 23.3% (95% CI −54.7 to 7.9) and 22.3% (95% CI −71.2 to 26.6) during HD in groups I and II and increased ($P <$ 0.05) by 43.5% (95% CI 10.3 to 76.7) and 46.8% (95% CI 10.3 to 83.3) in groups III and IV, respectively. The changes in PTH (suppression or stimulation) were very closely related to changes in iCa (Fig. 1). The predialysis values as well as the intradialytic changes of all other biochemical parameters measured did not differ in the four treatment groups (Table 1). A significant decrease in serum K, Cl, P, BUN, and creatinine, and a significant increase in pH and HCO_3 were seen during HD, whereas PCO_2, serum Na, and albumins remained unchanged. Intradialytic changes in iMg were correlated among all laboratory parameters measured only to those of sMg ($r =$ 0.75; $P < 0.05$). Finally, intradialytic fluid removal was similar between treatments groups (Table 1).

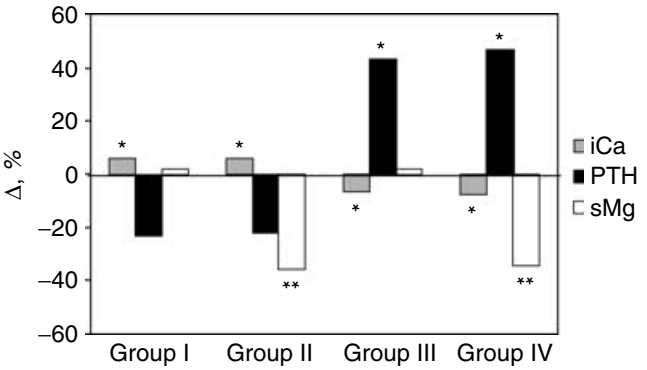

Fig. 1. Percent changes in serum magnesium (sMg), ionized serum calcium (iCa), and serum parathormone (PTH) in the four treatment groups during hemodialysis. $^{*}P < 0.05$; $^{**}P < 0.001$.

Hemodynamic indices were similar prior to the treatments (Table 2). As shown in Figure 2, BP decreased to

Table 2. Baseline (predialysis) hemodynamic data in groups I, II, III, and IV of study A ($N = 8$) and in the high (0.75 mmol/L) dialysate magnesium (HdMg) group, medium (0.5 mmol/L) dialysate magnesium (MdMg) group, and low (0.25 mmol/L) dialysate magnesium (LdMg) group of study B ($N = 14$)

Parameter	Study A			
	Group I	Group II	Group III	Group IV
SBP *mm Hg*	135.8 ± 13.6	133.6 ± 21.3	132.9 ± 28.3	135.0 ± 19.7
DBP *mm Hg*	69.4 ± 10.5	69.6 ± 11.5	66.6 ± 11.8	68.0 ± 7.0
MAP *mm Hg*	91.5 ± 13.8	91.0 ± 12.9	88.7 ± 15.8	90.3 ± 7.6
CI *L/min/m²*	3.55 ± 1.24	3.37 ± 1.30	3.39 ± 0.95	3.43 ± 1.09
SI *mL/m²*	44.3 ± 15.7	41.9 ± 16.4	43.6 ± 15.5	45.7 ± 18.2
HR *bpm*	81.3 ± 13.8	83.0 ± 20.3	80.0 ± 13.9	78.1 ± 13.9
TPRI *dyn.sec/cm⁵/m²*	2275 ± 836	2417 ± 958	2218 ± 719	2313 ± 806
Parameter (Average of 12 sessions)	Study B			
	HdMg	MdMg	LdMg	
SBP *mm Hg*	130.0 ± 9.3	129.1 ± 9.6	129.5 ± 10.6	
DBP *mm Hg*	76.2 ± 10.3	76.0 ± 9.2	75.7 ± 9.2	
MAP *mm Hg*	94.1 ± 9.3	93.8 ± 8.8	93.6 ± 8.7	
HR *bpm*	79.2 ± 10.7	78.7 ± 11	79.5 ± 11	

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CI, cardiac index; SI, stroke index; HR, heart rate; bpm, beats per minute; TPRI, total peripheral resistance index. Data are expressed as mean ± SD.

a greater extent in group IV compared to the other three groups, in which BP fell similarly. MAP, averaged across time, decreased by 15.2% (95%CI −19.8 to −10.7) in treatment group IV, whereas it dropped by 6.3% (95% CI −12 to −0.6), 4.2% (95% CI −9 to 0.6), and 6.2% (95% CI −12.9 to 0.5) in the groups I, II, and III, respectively. The intrasession changes of both SBP and DBP were analogous to MAP. The treatment effect ($P < 0.05$) and the time effect ($P < 0.001$) for SBP, DBP, and MAP were statistically significant. There was also a time × treatment interaction effect for SBP ($P < 0.01$) and MAP ($P < 0.05$), but not for DBP. Conceptually, the interaction term can be considered as a test to show whether or not two or more factors relate with each other. Accordingly, the presence of a time × treatment interaction effect for SBP, and MAP suggested that the effect of treatment depended on time. This interaction (or relationship) between time and treatment is depicted in Figure 2, where SBP and MAP decreased significantly to a much greater extent in treatment group IV than in the other groups during the second half of HD. On the contrary, changes (decrease) in DBP did not differ significantly among the four treatment groups across time periods during HD, findings implying the absence of an interaction between time and treatment. The profile of CI and stroke index (SI) changes was similar to that of MAP (Fig. 2). Both mean CI and SI reductions over time by 12.1% (95% CI −21.6 to −2.6) and 17% (95% CI −28.4 to –5.7), respectively, in group IV, were significantly greater from that in group I and III, but not from that in group II. The treatment effect ($P < 0.05$) and the time × treatment effect for CI ($P < 0.05$) and SI ($P < 0.001$) were statistically significant, and a time effect for CI ($P < 0.01$) was present only in treatment group IV. Given that TPRI remained unchanged in group IV, it is apparent that the blood pressure effect in that group was primarily due to changes in cardiac output through analogous changes in stroke volume. Overall, intradialytic TPRI alterations were less pronounced than the corresponding CI alterations. TPRI did not increase in any group. The maximum reduction in TPRI, averaged across time, observed in group III (5.4%; 95% CI −12.9 to 2.1) differed significantly ($P < 0.05$) from the minimum one seen in group II (0.13%; 95% CI −10.2 to 9.9), but the treatment effect was not statistically significant. Finally, there was not a treatment effect for HR, which increased significantly ($P < 0.05$) with time in groups II, III, and IV by 5.3% (95% CI 0.2 to 10.3), 4.5% (95% CI −1.4 to 10.4), 6% (95% CI −2.4 to 14.5), respectively, but not in group I (3.3%; 95% CI 0 to 6.6).

Study B

The mean pre- and post-HD sMg and iCa levels, as well as body weights, in the three treatment groups are presented in Table 3. The mean pre-HD sMg level (1.21 ± 0.12 mmol/L, range 0.99 to 1.37) in the HdMg group was significantly higher ($P < 0.001$) than that seen in both MdMg (1.06 ± 0.11 mmol/L, range 0.88 to 1.28) and LdMg (0.91 ± 0.13 mmol/L, range 0.7 to 1.07) groups. Hypermagnesemia (sMg >1.1 mmol/L) was observed in nine (64%) and five (36%) out of 14 patients in the HdMg and MdMg groups, respectively, while it was absent in the LdMg group. sMg decreased by 0.1% (95% CI −4.1 to 3.9), 12.9% (95% CI −15.8 to −10) and 26.1% (95% CI −29.9 to −22.3) during HD in the HdMg, MdMg, and LdMg groups, respectively. Mean pre-HD iCa levels did not differ among the treatment groups, and the iCa levels decreased ($P < 0.01$) equally about 3% (95% CI −5 to −1) with all treatments. Mean (four-week) pre-HD weights and the mean fluid loss during HD were comparable in the three treatment groups.

Mean predialysis BP and HR did not differ among treatment groups (Table 2). The treatment effect was significant for SBP ($P < 0.05$), DBP ($P < 0.05$), and MAP ($P < 0.05$), and there was a time × treatment interaction effect for DBP ($P < 0.05$) and MAP ($P < 0.05$). SBP, DBP, and MAP decreased significantly ($P < 0.001$) with time in all treatment groups. There was no treatment or time × treatment interaction effect for HR. According to analysis across time points, depicted in Figure 3, intradialytic SBP decreased significantly ($P < 0.05$) with both LdMg and MdMg treatments compared to HdMg treatment. DBP fell significantly with LdMg treatment compared to MdMg ($P < 0.05$) and HdMg ($P < 0.01$) treatments. Finally, MAP fell to a greater extent ($P < 0.01$) with LdMg

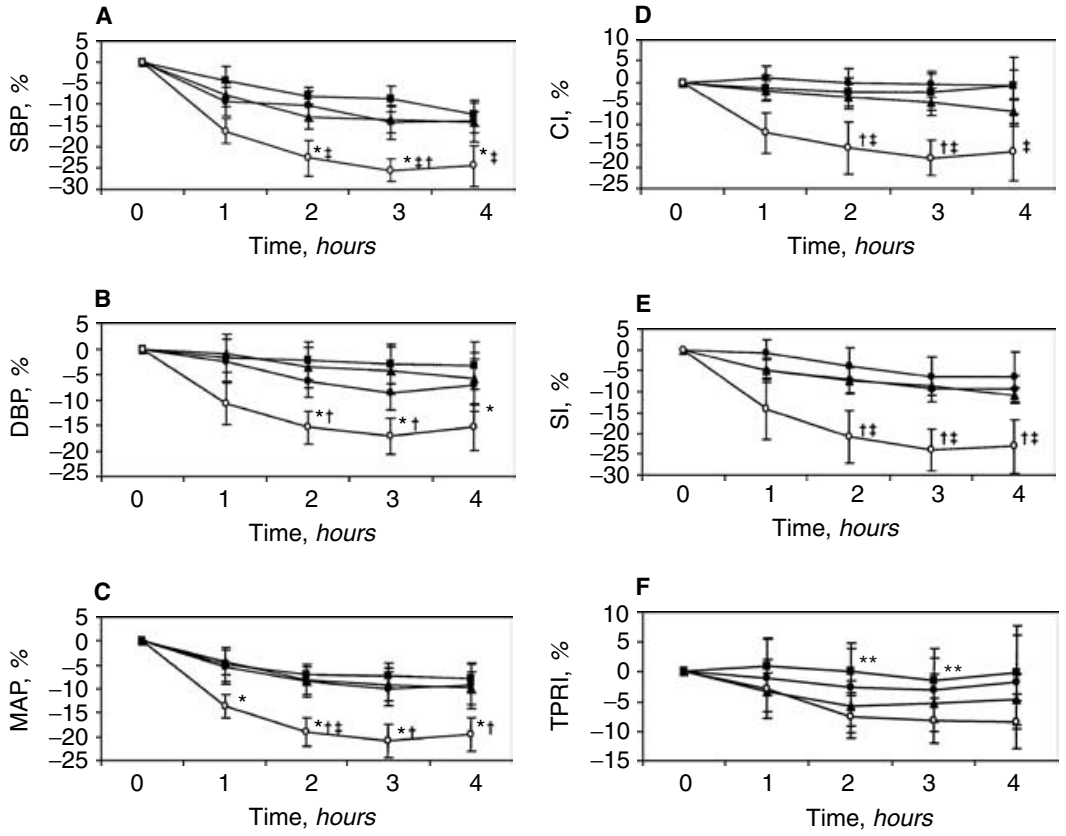

Fig. 2. Hourly intradialytic percent changes in (*A*) systolic blood pressure (SBP), (*B*) diastolic blood pressure (DBP), (*C*) mean arterial pressure (MAP), (*D*) cardiac index (CI), (*E*) stroke index (SI), and (*F*) total peripheral resistance index (TPRI). (▲) Group I, (■) group II, (●) group III, (○) group IV. †Significant difference between group IV and group I. *Significant difference between group IV and group II. ‡Significant difference between group IV and group III. **Significant difference between group II and group III. Data points represent mean values ± SEM. Study A, $N = 8$.

Table 3. Pre-HD and post-HD data of biochemical parameters and body weight in the high (0.75 mmol/L) dialysate magnesium (HdMg) group, medium (0.5 mmol/L) dialysate magnesium (MdMg) group, and low (0.25 mmol/L) dialysate magnesium (LdMg) group of study B

	HdMg		MdMg		LdMg	
Parameter	Pre-HD	Post-HD	Pre-HD	Post-HD	Pre-HD	Post-HD
iCa *mmol/L*	1.17 ± 0.06	1.13 ± 0.03[a]	1.18 ± 0.08	1.14 ± 0.04[a]	1.16 ± 0.07	1.12 ± 0.04[a]
sMg *mmol/L*	1.21 ± 0.12[c]	1.20 ± 0.08	1.06 ± 0.11[d]	0.92 ± 0.09[b]	0.91 ± 0.13	0.67 ± 0.07[b]
BW *kg*	65.5 ± 12.3	63.4 ± 12.1[b]	65.6 ± 12.2	63.4 ± 12.1[b]	65.5 ± 12.2	63.6 ± 11.9[b]

Abbreviations can be found in Table 1. Data are expressed as mean ± SD.
[a] $P < 0.01$ vs. pre-HD; [b] $P < 0.001$ vs. pre-HD; [c] $P < 0.001$ vs. MdMg and LdMg; [d] $P < 0.001$ vs. LdMg.

than with HdMg treatment. Interestingly, the intradialytic MAP drop by 8.1% (95% CI −10.7 to –5.5), 9.5% (95% CI −12.2 to –6.7), and 10.7% (95% CI −13.2 to −8.2) in the HdMg, MdMg, and LdMg, respectively, varied with the sMg drop, described above, in the corresponding groups. This positive correlation between the magnitude of BP and sMg reduction observed further emphasized the critical role of differentiated dMg concentration on the cardiovascular function.

Differences in intradialytic events between the three treatment protocols are shown in Table 4. There were significant ($P < 0.05$) differences in symptomatic hypotension among the three treatment groups. The percentage of sessions with symptomatic hypotension in the HdMg treatment group was significantly lower (4.2% vs. 10.7%) than that in the LdMg treatment group. The corresponding proportion of hypotensive sessions in the MdMg treatment group was almost twice as higher than that in the HdMg treatment group (7.7% vs. 4.2%). However, this difference did not reach statistical significance. There were fewer episodes of asymptomatic hypotension ($P < 0.05$) and total (symptomatic and asymtomatic) hypotension ($P < 0.001$) with HdMg as compared to both LdMg and MdMg treatments.

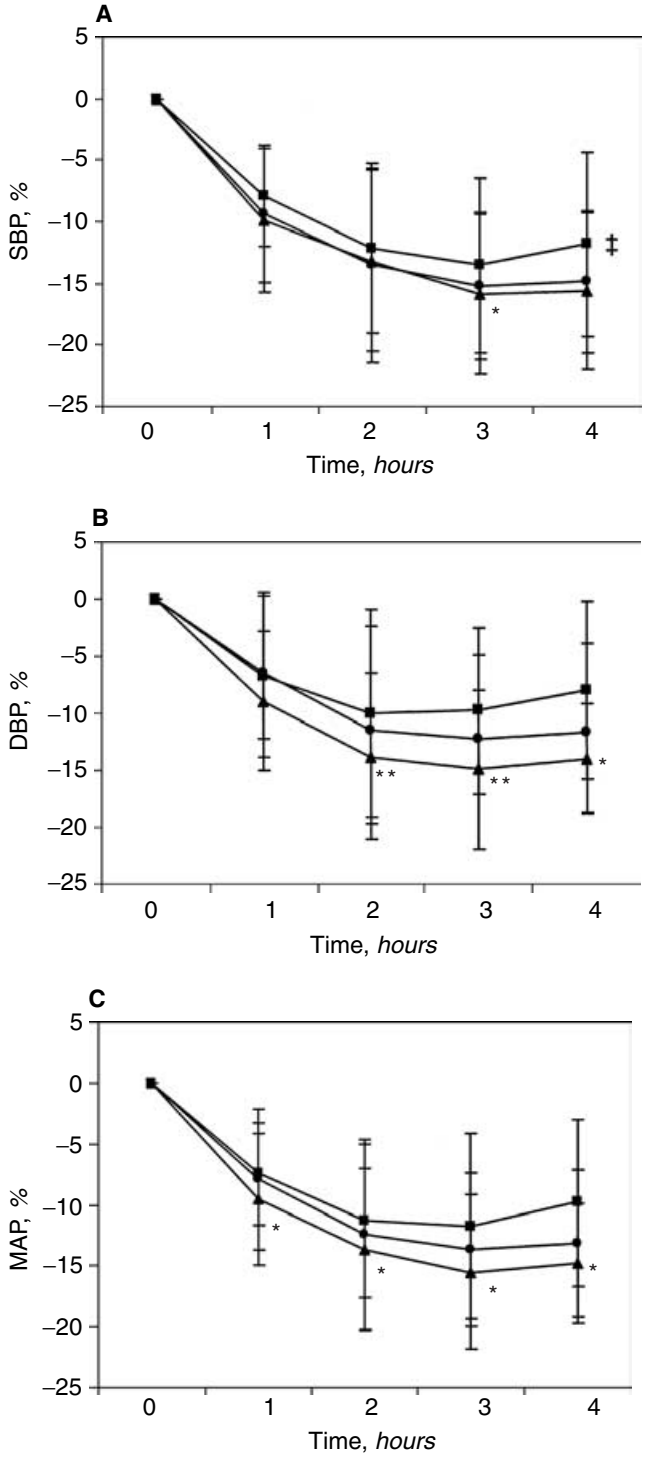

Fig. 3. Hourly intradialytic percent changes in (*A*) systolic blood pressure (SBP), (*B*) diastolic blood pressure (DBP), and (*C*) mean arterial pressure (MAP). (■) High (0.75 mmol/L) dialysate magnesium (HdMg), (●) medium (0.5 mmol/L) dialysate magnesium (MdMg), (▲) low (0.25 mmol/L) dialysate magnesium (LdMg). *Significant difference between LdMg and HdMg groups. **Significant difference between LdMg and both MdMg and HdMg groups. ‡Significant difference between HdMg and both MdMg and LdMg groups. Data points represent mean values ± SD. Study B, $N = 14$.

DISCUSSION

Our results showed that intradialytic changes in sMg played an important and independent role on systemic hemodynamics only when HD was performed with a low 1.25 mmol/L dCa. No such role of sMg was apparent, or even if present was not detected, during HD with a high 1.75 mmol/L dCa. Indeed, the most important findings of the hemodynamic study were that a dialysate formulation containing Mg and Ca concentrations of 0.25 mmol/L and 1.25 mmol/L, respectively, emerged as an important cause of IDH, and during HD with 1.25 mmol/L dCa, BP was preserved better with a high dMg of 0.75 mmol/L compared to a low one of 0.25 mmol/L. Before we proceed to the interpretation of these intriguing findings, resulting from concomitant changes in sMg and iCa, it is appropriate to briefly state the available evidence regarding the hemodynamic effects of changes in magnesemia and calcemia individually.

Changes in iCa. Modest variations in iCa are correlated with clinically significant changes in myocardial contractility. A number of recent investigations showed a significant decrease of blood pressure during HD with the use 1.25 mmol/L dCa as compared to 1.75 mmol/L dCa, in both healthy [10, 17] and cardiac-compromised HD patients [11]. Conversely, an intradialytic increase in iCa, as it occurs with the use of high dCa concentrations, results in a measurably higher intradialytic BP compared to a dCa of 1.25 mmol/L due to an iCa-induced increase in myocardial contractility [3–4], and thus, increasing the dCa concentrations has been advocated as a means to protect against intradialytic hypotension [11, 17].

Changes in sMg.

Hypomagnesemia. The majority of the in vitro experiments in isolated ventricular tissue or myocytes record an inverse relation between Mg concentration and inotropic response, mediated probably by the antagonistic actions between Mg and Ca [18–20]. Paradoxically, myocardial contractility is usually compromised in animals on Mg-deficient diet [21], or on perfusion of whole heart [22] with low Mg (0.3 mmol/L) buffer. Mg deficiency–induced coronary vasospasm [23], defective energy metabolism [24], and excessive free radical generation [25] may be important variables acting in concert or independently to affect myocardial function. Despite the important role of Mg deficiency or hypomagnesemia in the etiology of cardiovascular pathology [9], the mechanisms by which hypomagnesemia might lead to myocardial dysfunction still remain unclear.

Hypermagnesemia. It has been systematically shown that magnesium salt infusion lowers BP via a reduction of TPR despite a moderate increase in cardiac output [8, 26–28]. The latter is accomplished via increases in HR and coronary flow [27] or a direct myocardial effect [28–29], independent of changes in preload, afterload, heart rate, or flow [29]. These Mg-induced direct or indirect

Table 4. Intradialytic symptoms, during 168 hemodialysis sessions, with high (0.75 mmol/L) dialysate magnesium (HdMg) treatment, low (0.25 mmol/L) dialysate magnesium (LdMg) treatment and medium (0.5 mmol/L) dialysate magnesium (MdMg) treatment

	Treatment			*P* value		
Symptom	HdMg *N* (%)	LdMg *N* (%)	MdMg *N* (%)	HdMg vs. LdMg	HdMg vs. MdMg	LdMg vs. MdMg
Symptomatic hypotension	7 (4.2)	18 (10.7)	13 (7.7)	0.019	>0.1	>0.1
Asymptomatic hypotension	11 (6.5)	26 (15.4)	24 (14.3)	0.009	0.026	>0.1
Total hypotension	18 (10.7)	44 (26.2)	37 (22.0)	0.001	0.004	>0.1

vasodilatory effects are dose dependent [27] and can be elicited at plasma concentrations as low as 1.38 mmol/L [28], while a concentration of 1.8 to 3.0 mmol/L has been suggested for treatment of eclamptic convulsions [27].

According to our data, the substantial intradialytic fall of BP seen with a HD solution containing Mg and Ca concentrations of 0.25 mmol/L and 1.25 mmol/L, respectively, was due to an unusual impairment of myocardial contractility not compensated by an increased TPR. With all other HD parameters standardized, this formulation resulted in hypomagnesemia and hypocalcemia by decreasing sMg and iCa by 35% and by 7.7%, respectively, situations shown to impact unfavorably on cardiac performance. Thus, the combined cardiodepressant effects of both hypomagnesemia and hypocalcemia was, most probably, the basis for this unexpected myocardial dysfunction. Supported of this, the harmful effects on cardiac function and BP detected with this HD formulation were not seen with other formulations causing either only hypomagnesemia (group II) or only hypocalcemia (group III). Given that Mg is a naturally occurring calcium channel inhibitor, it is understandable that with a subnormal level of Mg, the cardiovascular contractility increases or decreases when the extracellular Ca is raised or lowered, respectively.

Following fluid removal from the circulating blood volume by UF, refilling occurs from the extravascular compartment, which, by avoiding hypovolemia, serves as an important compensatory mechanism to preserve BP stability. Plasma volume changes were not monitored in the present study, so we cannot rule out inadequate vascular refilling as the cause of the cardiac output reduction seen in the low dCa and dMg group of patients. However, factors known to affect substantially plasma refilling rate, including fluid overload, ultrafiltation rate, plasma albumin levels, dialysate sodium concentration, or dialysate temperature were similar in all treatment groups, findings that make this possibility unlikely.

In treatments that combine utilization of diffusion and convection, there is a continuous interference between these two transport mechanisms. Given the high-diffusive coefficients of the ionized and complexed forms of Mg and Ca in serum, convection transport has little influence on the diffusive balance of Mg and Ca, respectively. In addition, the convective loss of the ultrafilterable blood Mg and Ca, because it is limited to the weight loss in both low- and high-flux HD, apparently contributes equally to the overall Ca and Mg balance, respectively, in both treatment modalities. A number of studies have shown that during both low-flux [30–31] and high-flux hemodialysis [32–33], intradialytic changes in serum Mg and Ca depended mainly on their respective concentration gradients between dialysate and pretreatment serum levels, irrespective of the UF volume, blood flow, and dialysis efficiency [30–31]. Thus, in all likelihood, comparable intradialytic changes in both iCa and sMg, and, consequently, hemodynamic profiles would have been attained if high-flux dialyzers had been utilized instead of low-flux dialyzers in the present study. With regard to hemodiafiltration (HDF), the much higher UF volumes (up to 40 to 50 L) in comparison to conventional HD may considerably affect the diffusive transport of Ca and Mg. In addition, the infusion mode (predilution and postdilution HDF), as well as the variable Ca and Mg concentrations of the infusional fluids, may further influence dialytic Mg and Ca balances. Thus, different HDF protocols can produce either positive or negative Ca and Mg fluxes during treatment. Further prospective studies are needed to investigate the role of simultaneous hypocalcemia and hypomagnesemia on cardiovascular stability in mixed diffusive-convective treatments.

Treatment with a dMg level of 0.25 mmol/L or lower has been generally used either to prevent and treat Mg overload in HD patients, or as means to afford giving Mg containing P binders to control hypercalcemia associated with the use of calcium salts and vitamin D in the treatment of secondary hyperparathyroidism. In the relevant studies [31, 34], however, where a low 0.25 mmol/L dMg was used in conjunction with a low dCa mmol/L, hemodynamic data are not provided for comparison.

The other most important finding of our hemodynamic study was that during HD with 1.25 mmol/L dCa, the use of a high dMg of 0.75 mmol/L prevented the BP fall seen with a low dMg of 0.25 mmol/L. According to our results, a trivial increase in sMg by 2%, induced by a 0.75 mmol/L dMg, resulted in a less than 6.3% reduction in mean MAP associated with an analogous minor decrease in mean TPRI and a constant CI. Actually, sMg increased only in half of the patients, whereas it decreased in the other half of them. It is possible that if

a higher dMg level had been used, the ensuing higher degree of hypermagnesemia could have resulted in a more marked vasodilatory hypotension. However, dMg concentrations higher than 0.75 mmol/L are not used in routine HD because of the risk of developing hazardous hypermagnesemia. Conclusively, the use of a high 0.75 mmol/L dMg had no impact on TPR, irrespective of the concomitant dCa concentration. Interestingly, analogous changes in TPR were also seen with 0.25 mmol/L dMg. These findings may help to substantiate the biologic rationale why increasing the concentration of Mg in the dialysate during HD with 1.25 mmol/L dCa would improve intradialytic hemodynamics, and thus, blood pressure stability. In the event that the unfavorable effects of hypomagnesemia were additive to those of hypocalcemia on cardiac function, an assumption that must be verified, then the use of 0.75 mmol/L (group III) instead of 0.25 mmol/L dMg (group IV) by circumventing hypomagnesemia, or even causing a trivial hypermagnesemia, apparently exerted a beneficial role on cardiac performance. Thus, with similar nonsignificant changes in TPR induced by both 0.75 mmol/L and 0.25 mmo/L dMg treatments, the significantly better preservation of CI seen with 0.75 mmol/L dMg as compared to 0.25 mmol/L dMg treatment presents a plausible explanation why increasing dMg may prevent IDH during HD with a low dCa of 1.25 mmol/L.

Notwithstanding, because of the opposing effects of Mg and Ca on the cardiovascular system, the potential role of Mg on systemic hemodynamics during HD cannot be definitely judged when iCa is not maintained constant. In this context, we were justified in opting to use two different dCa levels to overcome this problem. The role of dMg level on the intradialytic BP, obscured by utilizing a high 1.75 mmol/L dCa, became evident upon using a low dCa of 1.25 mmol/L. In the presence of almost identical iCa and PTH modifications in groups III and IV groups (Fig. 1), two totally distinct intradialytic BP profiles emerged (Fig. 2), owing exclusively to the use of two different dMg concentrations in the two groups. In addition, these data indicated that PTH changes did not impact on intradialytic BP response, although the prevailing effects of sMg and iCa on the cardiovascular function could have masked such an effect. Factors other than dMg and dCa might possibly have played a role in the BP changes reported in the hemodynamic study. However, differences among study groups were not found with respect to acid-base parameters, toxin removal, electrolyte alterations, and fluid removal. The absence of significant changes in these factors strengthens our notion that the hemodynamic modifications observed were dependent solely on the concurrent changes in serum Mg and Ca. One could doubt an independent hemodynamic effect of Mg by arguing, for example, that the low Mg effect may have been mediated by changes in iCa due to an Mg-Ca interaction lowering iCa during the diffusive therapy. However, the findings that (*1*) the intradialytic variations in factors, including pH, serum phosphorus, and albumins, that could potentially affect the ratio of ionized/total Mg (iMg/sMg) and ionized/total Ca (iCa/sCa) [30] did not differ in the four treatment groups, (*2*) the iMg/sMg and iCa/sCa ratios were maintained constant (about 70% and 50%, respectively) with all four different combinations of Mg and Ca in the dialysate (Table 1), and (*3*) the intradialytic changes in iMg did not correlate to corresponding changes in iCa, are against this hypothesis. Therefore, these results further support a Ca-independent, hemodynamic role of Mg during HD.

Based on our results, we reasoned that increasing dMg concentration could prevent or ameliorate the IDH associated with a low 1.25 mmol/L dCa [10–11, 17]. We tested this hypothesis in our short-term chronic study (study B), and it was found to be correct. Overall, BP remained significantly higher with 0.75-mmol/L dMg treatment compared to both 0.5 mmol/L and 0.25 mmol/L dMg treatments. The superior hemodynamic stability detected with the use of high 0.75 mmol/L dMg was translated into a significantly reduced incidence of total hypotension (symptomatic and asymptomatic) in the high dMg treatment group as compared to both 0.5 mmol/L and 0.25 mmol/L dMg treatment groups, as mentioned in **Results**. The mean pre- and post-HD values of sMg in all three treatment groups (Table 3) were similar to the corresponding values of sMg in previous studies [30, 35], where treatment was performed with the same dMg concentrations, respectively. With regard to the incidence of hypermagnesemia, sMg slightly increased (less than 1.37 mmol/L) above the upper limit of normal (1.1 mmol/L) in nine (64%) out of 14 patients in the high dMg group, and five (36%) in the medium dMg group.

The only available study in which the impact of dMg level on intradialytic BP was examined [abstract; Rakash et al, *J Am Soc Nephrol* 7:1238A, 1996] gave somewhat contradictory results. In that study, 78 HD patients were randomly assigned to one of the four treatment groups with dialysate containing either citrate or bicarbonate buffer with a low 0.38 mmol/L dMg or a high 0.75 mmol/L dMg. Patients treated with the high dMg experienced a larger intradialytic fall in MAP and greater incidence in intradialytic hypotension than patients treated with the low dMg (-28 ± 4 mm Hg vs. -16 ± 4 mm Hg and 61.9% vs. 28.5%, respectively). Similar results were obtained also with acetate as a buffer. The reasons for this discrepancy are unknown, but differences in the magnitude of intradialytic changes in sMg in either direction (increase or decrease), or possibly the variation in other hemodialysis parameters between these two studies, are potential explanations.

The interesting findings of the present study, if confirmed by future investigations, might have clinical

implications with regard to dialysis tolerance. First, treatment with HD solutions containing 1.25 mmol/L dCa and low dMg concentrations, shown to be a potential risk factor for IDH by this pilot study, should be avoided, especially in IDH-prone patients with impaired cardiovascular function. Second, the use of high dMg concentrations may be thought as a simple maneuver to prevent IDH in patients treated with low dCa levels. Accordingly, patients who manifest hemodynamic instability during HD with 1.25 mmol/L dCa may benefit upon switching from a low 0.25 mmol/L or medium 0.5 mmol/L dMg to a high one of 0.75 mmol/L. This substantiated favorable hemodynamic effect may play a more critical role in cardiovascular compromised patients because it can prevent further deterioration, or even enhance cardiac performance in these patients when challenged with adverse hemodynamic conditions. Further studies are needed to verify this assumption. We opted not to include patients with severely compromised left cardiac function in our study to avoid confounding our results. However, any possible hemodynamic benefits attained during HD by using high dMg must be weighted against the long-term consequences of such a treatment [36], including those related to bone metabolism [37–40]. For example, chronic hypermagnesemia, due to its suppressive effect on PTH secretion, may potentially prevent aggravation of secondary hyperparathyroidism seen upon using 1.25-mmol/L dCa [41], while suppression of PTH in the long run could be a risk factor for the development of adynamic bone disease [37–38].

CONCLUSION

We identified a dialysis solution containing 0.25 mmol/L Mg and 1.25 mmol/L Ca as a significant risk factor for developing IDH, and, as such, its use should be avoided in IDH- prone individuals, especially cardiac-compromised patients, and we provided strong evidence that increasing dMg to 0.75 mmol/L could effectively prevent BP deterioration frequently seen in patients treated with a low 1.25 mmol/L dCa. Thus, manipulating dMg levels independently or in concert with dCa levels might have important implications with regard to dialysis tolerance. For this reason, the potential role of the dMg on the cardiovascular system during HD requires further investigation.

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